# The Latest in Alzheimer's and Dementia Science: A New Phase of Research, Treatment and Care

Rebecca M. Edelmayer, Ph.D.
Sr. Director, Scientific Engagement
Medical & Scientific Relations
Alzheimer's Association

# 2023 ALZHEIMER'S DISEASE FACTS AND FIGURES

While only 4 in 10 Americans talk to their doctor right away when experiencing early memory or cognitive loss,

7 in 10 would want to know early if they have Alzheimer's disease if it could allow for earlier treatment.

More than
**6 million Americans**
are living with Alzheimer's

.....a number expected to
**double** by 2050

In 2023, Alzheimer's and other dementias will cost the nation
**$345 billion**

By 2050, these costs could rise to nearly
**$1 trillion**

**Over 11 million Americans**
provide unpaid care for people with Alzheimer's or other dementias

These caregivers provided more than 18 billion hours valued at nearly
**$340 billion**

Between 2000 and 2019, deaths from heart disease has
**decreased 7.3%**

while deaths from Alzheimer's disease have
**increased 145%**

**1 in 3**
seniors dies with Alzheimer's or another dementia

It kills more than
**breast cancer + prostate cancer**
combined

The lifetime risk for Alzheimer's at age 45 is
**1 in 5** for women
**1 in 10** for men

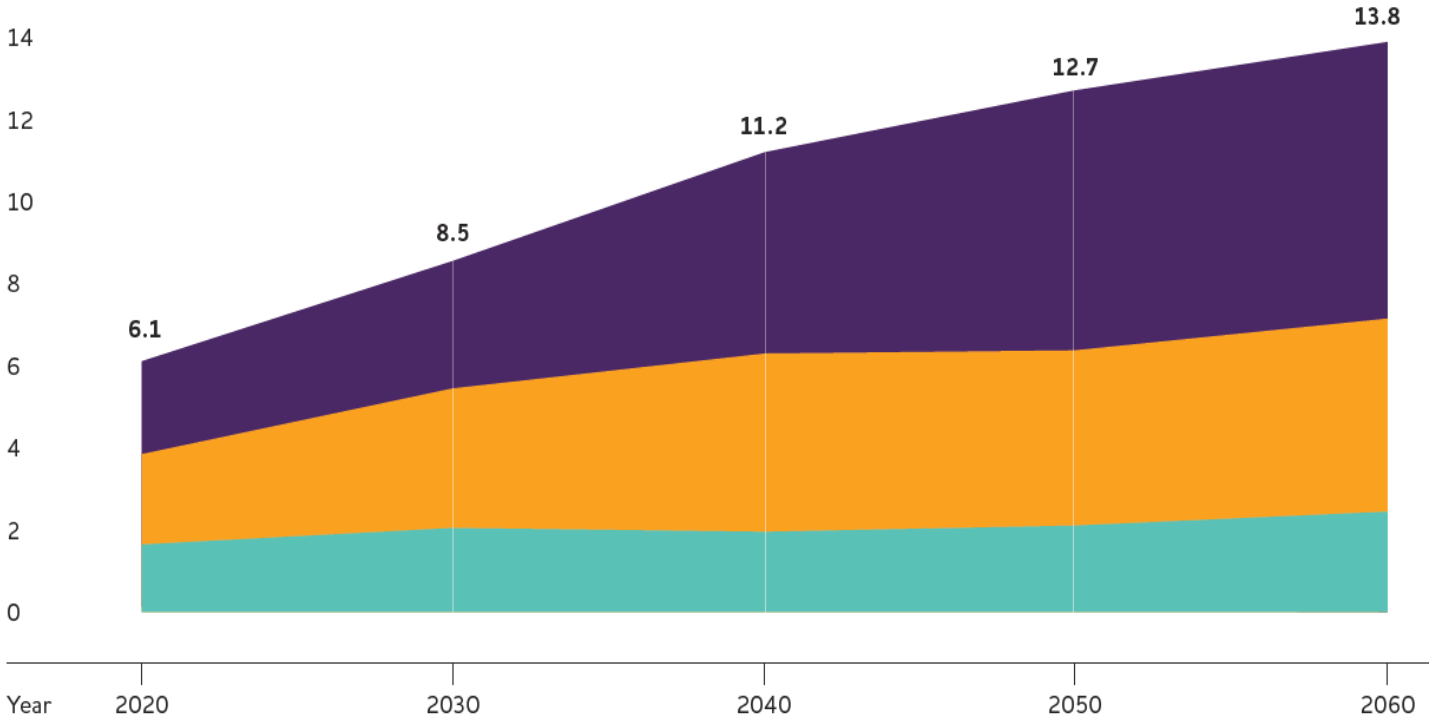
ALZHEIMER'S ASSOCIATION®

# Prevalence

An estimated **6.7 million Americans** are living with Alzheimer's dementia.

The number of Americans **65+** living with Alzheimer's is expected to nearly **double by 2050.**

Projected Number of People Age 65 and Older (Total and by Age) in the U.S. Population with Alzheimer's Dementia, 2020 to 2060




Created from data from Rajan et al.[A5,216]

# Gender and Racial Differences in Alzheimer's Prevalence

Almost **two-thirds** of Americans with Alzheimer's are **women**

Older **Blacks/African Americans** and **Hispanics/Latinos** are disproportionately **more likely** than older non-Hispanic Whites to have Alzheimer's or other dementias

Population-based studies for other racial/ethnic groups are needed

# What May Impact Risk of Cognitive Decline or Dementia


**Constellation of reasons may be fundamental and unique to each individual**

**Social determinants of health may impact some or all of these factors**

**Strength of our understanding is different across risk factors**

**Need to Study Risk from ALL Angles**

# Causes of Cognitive Impairment

## Currently Irreversible

### Neurodegenerative

Nerve cell death selective for cognitive networks

- Alzheimer's Disease
- Lewy Body Disease
- Frontotemporal Disorders
- Huntington's Disease
- Parkinson's Disease

### Vascular

- Stroke
- Small vessel disease
- Micro-bleeds
- Blockage of vessels

## Potentially Reversible

### Rarer Causes

- Metabolic
- Toxicity (including alcohol)
- Vitamin deficiencies
- Tumor lesion
- Medication side effect
- Sleep disturbance

# Clinical Symptoms of Dementia

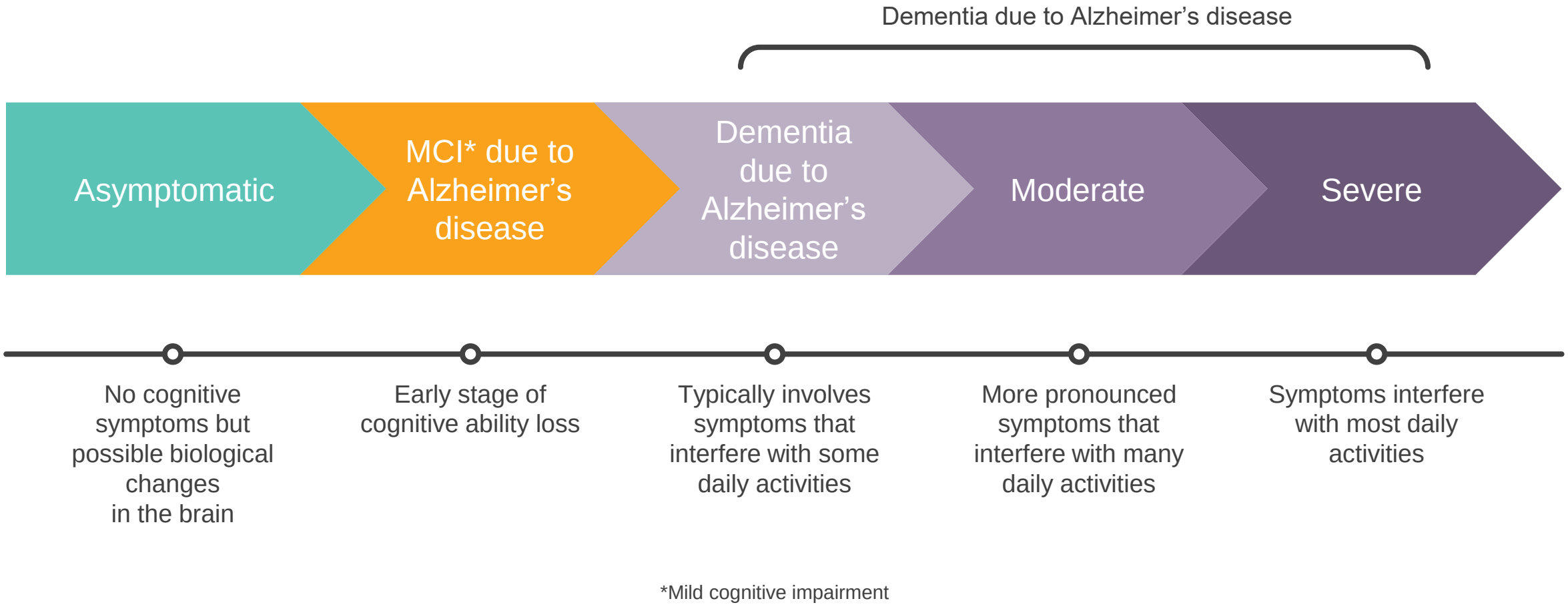
## COGNITIVE

- Memory
- Learning
- Thinking
- Planning

## NON-COGNITIVE (BEHAVIORAL & PSYCHOLOGICAL)

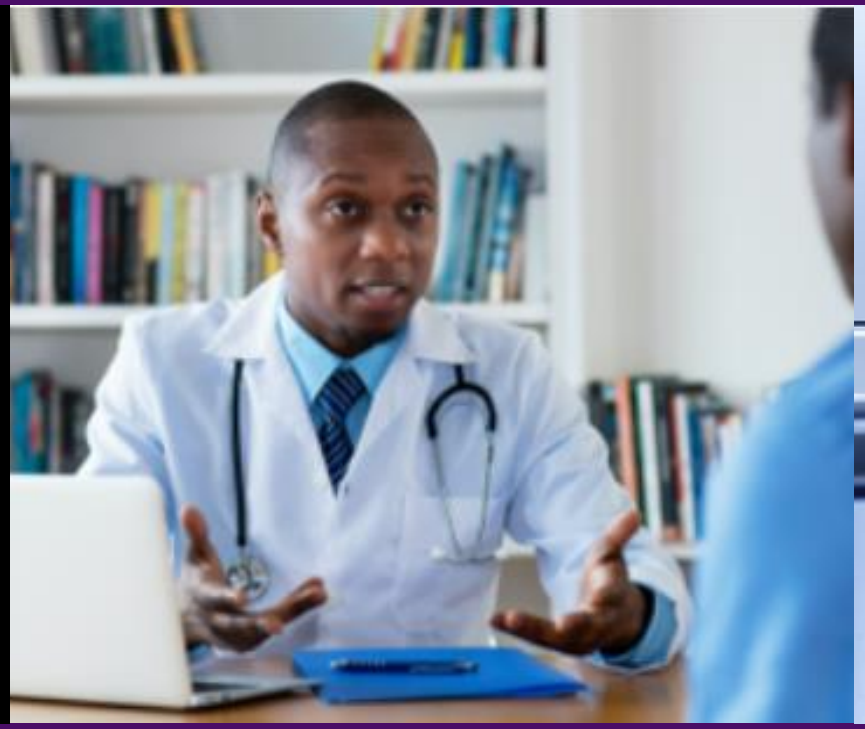
- Personality changes
- Depression
- Anxiety
- Delusions
- Hallucinations
- Apathy
- Agitation
- Sleep disturbances

# Alzheimer’s Disease is a Continuum




*Mild cognitive impairment

# Early Detection and Diagnosis



## An early diagnosis can have emotional, social and medical benefits

- Understand symptoms
- Explore treatment options
- Improve health outcomes
- Prevent complications
- Make legal and financial decisions
- Access care services
- Participate in clinical trials
- Effectively manage the cost of care

# Revising the Diagnostic Guidelines for Alzheimer's and MCI

1984 → 2001 → 2011 → 2018

ELSEVIER

CrossMark

Alzheimer's & Dementia 14 (2018) 535-562

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

## NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

**Contributors**[†]: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

[a]*Department of Radiology, Mayo Clinic, Rochester, MN, USA*
[b]*Department of Neurological Sciences, Rush University, Chicago, IL, USA*
[c]*Department of Psychiatry and Neurochemistry, University of Gothenburg, Gothenburg, Sweden*
[d]*Medical & Scientific Relations, Alzheimer's Association, Chicago, IL, USA*
[e]*Office of Drug Evaluation, FDA, Silver Spring, MD, USA*
[f]*Biogen, Cambridge, MA, USA*
[g]*Department of Neurology, Washington University, St. Louis, MO, USA*
[h]*Department of Public Health and Neuroscience, University of California Berkeley, Berkeley, CA, USA*
[i]*Department of Psychiatry, University of Cologne, Medical Faculty, Cologne, Germany*
[j]*Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA*
[k]*Prothena Biosciences, Inc., San Francisco, CA, USA*
[l]*BarcelonaBeta Brain Research Center, Pasqual Maragall Foundation and Hospital Clinic-IDIBAPS, Barcelona, Spain*
[m]*Department of Pathology, Stanford University, Standford, CA, USA*
[n]*Formerly at National Institute on Aging, Bethesda, MD, USA*
[o]*Department of Neurology, University of California San Francisco, San Francisco, CA, USA*
[p]*Department of Molecular Imaging, Austin Health, University of Melbourne, Melbourne, Australia*

Alzheimer's & Dementia

SPECIAL ARTICLE LEVEL OF RECOMMENDATION

## Practice guideline update summary: Mild cognitive impairment

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Ronald C. Petersen, MD, PhD, Oscar Lopez, MD, Melissa J. Armstrong, MD, MSc, Thomas S.D. Getchius, Mary Ganguli, MD, MPH, David Gloss, MD, MPH&TM, Gary S. Gronseth, MD, Daniel Marson, JD, PhD, Tamara Pringsheim, MD, Gregory S. Day, MD, MSc, Mark Sager, MD, James Stevens, MD, and Alexander Rae-Grant, MD

**Correspondence**
American Academy of Neurology
guidelines@aan.com

*Neurology*® 2018;90:126-135. doi:10.1212/WNL.0000000000004826

### Abstract

#### Objective

To update the 2001 American Academy of Neurology (AAN) guideline on mild cognitive impairment (MCI).

#### Methods

The guideline panel systematically reviewed MCI prevalence, prognosis, and treatment articles according to AAN evidence classification criteria, and based recommendations on evidence and modified Delphi consensus.

MORE ONLINE

**Podcast**
Dr. Jeff Burns talks with Dr. Ronald Petersen about the updated AAN guideline on mild cognitive impairment.
NPub.org/ojn0w9

# Need for Greater Diagnostic Accuracy

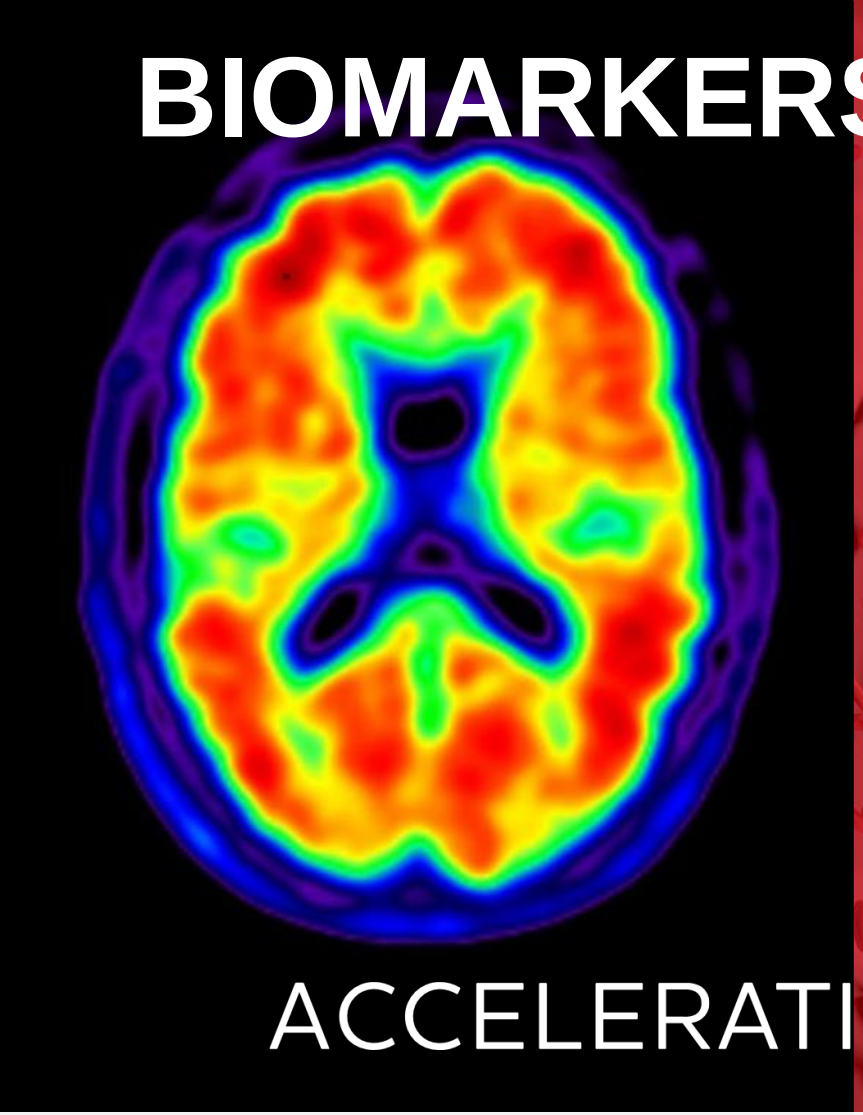
- 2011 NIA-AA Diagnostic Guidelines and 2018 NIA-AA Research Framework outlined more clearly the opportunities to increase the certainty of a diagnosis.
- This paired with the updated 2018 AAN guidance on all-cause MCI, and other evolving data tell us that the 1984 NINCDS-ADRDA diagnosis is effective and accurate about 70% of the time - and in those other instances, the use of biomarkers will increase the certainty.


*……of individuals clinically diagnosed as Alzheimer's disease dementia by experts **DO NOT** display Alzheimer's disease neuropathologic changes at autopsy or in brain scans*



*Nelson PT et al, Acta Neuropathol 2011*
*Rabinovici et al. JAMA. 2019*

# BIOMARKERS ARE CHANGING THE GAME



ACCELERATING THE SPEED OF RESEARCH

Brain Imaging

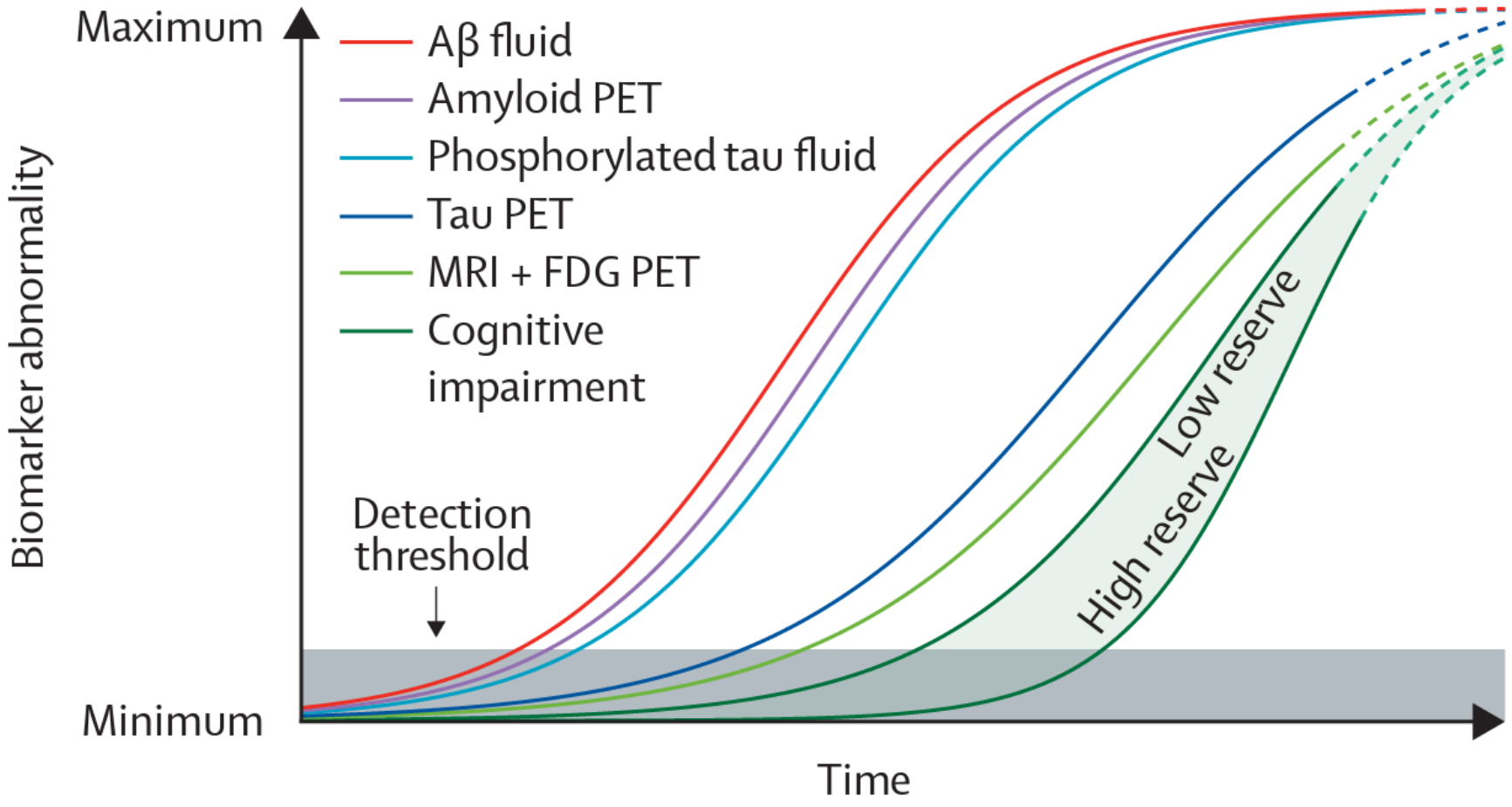
Biofluid Analysis

Emerging Markers

# Modernizing the Diagnosis

20

years or more before symptoms appear, the brain changes of Alzheimer's may begin.






*Adapted from Clifford Jack, Mayo Clinic*

# Translating Biomarker Results for the Patient: Quantification Matters and Informs Treatment and Care

## We are in the midst of a paradigm shift


## Quantification matters, Clinicians must answer questions:

- Am I at risk?
- What is my diagnosis?
- What stage is my disease?
- How fast will I progress?
- What treatments are appropriate?
- Is the treatment working?
- Can my dosing be adjusted?
- Can my treatment be stopped?
- What are my next steps?



*Weber, W.A. et al. The Future of Nuclear Medicine, Molecular Imaging, and Theranostics. J. Nuclear Medicine.2020*

# Revised Criteria For Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup

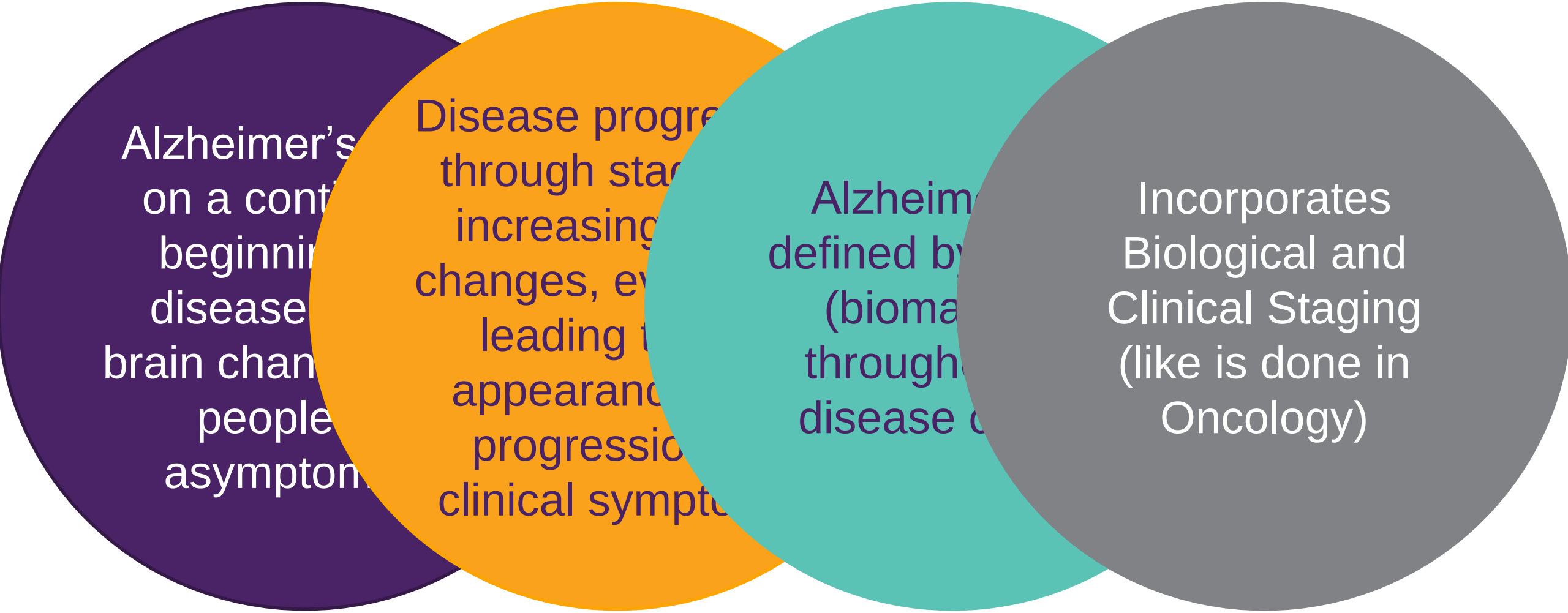

Charge is to examine the 2011 NIA-AA clinical guidelines and 2018 NIA-AA research framework in the context of the current scientific knowledge, and, if appropriate, revise the criteria for diagnosis and staging of Alzheimer's disease.

Workgroup members represent a broad and diverse range of scientific and medical expertise, including various institutions (public, academic and private) and professional organizations involved with Alzheimer's research and care.

Draft criteria were presented publicly at AAIC 2023, CTAD 2023, AD/PD 2024 and were open for public comments from the scientific community

**Revised criteria were submitted for publication in early 2024**

# Conceptual Foundation for Criteria



# Appropriate Use Criteria for Amyloid PET

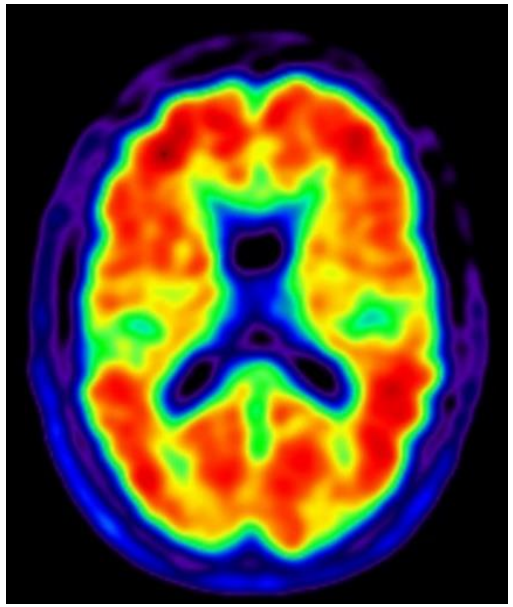
- International, multidisciplinary workgroup convened by Alzheimer's Association and SNMMI
- Preparing final manuscript for submission
- Publication Q2 of 2024

Alzheimer's & Dementia

Alzheimer's & Dementia 9 (2013) e1–e16

Appropriate use criteria for amyloid PET: A report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association

Keith A. Johnson[a], Satoshi Minoshima[b], Nicolaas I. Bohnen[c], Kevin J. Donohoe[d], Norman L. Foster[e], Peter Herscovitch[f], Jason H. Karlawish[g], Christopher C. Rowe[h], Maria C. Carrillo[i,*], Dean M. Hartley[i], Saima Hedrick[j], Virginia Pappas[j], William H. Thies[i]



Co-Chair
Gil Rabinovici, MD

Javier Arbizu, MD, PhD

Tammie Benzinger, MD, PhD

Kevin Donohoe, MD

Oskar Hansson, MD, PhD

Peter Herscovitch, MD

David Knopman, MD

Co-Chair
Keith Johnson, M.D.

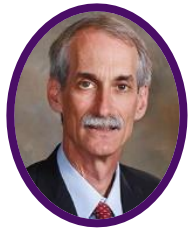
Phillip Kuo, MD, PhD

Jennifer Hagerty Lingler, PhD

Satoshi Minoshima, MD, PhD

Melissa E. Murray, PhD

Julie Price, PhD



Stephen Salloway, MD

# FDA Approved PET Markers

| | |
|---|---|
| 2000 | **FDA Approved Glucose PET Marker** |
| | • 18F-Fludeoxyglucose |
| 2012-2014 | **FDA Approved β-amyloid PET Markers** |
| | • 18F-Florbetaben (Neuraceq)<br>• 18F-Florbetapir (Amyvid)<br>• 18F-Flutemetamol (Vizamyl) |
| 2020 | **FDA Approved Tau PET Marker** |
| | • 18F-Flortaucipir (Tauvid) |

**Positron emission tomography (PET)** scan results aid doctors in diagnosing and treating memory conditions

# FDA Approved Cerebrospinal Fluid (CSF) Biomarkers

Lumipulse® G β-Amyloid Ratio (1-42/1-40)

**Abeta 42/40**

Elecsys® Phospho-Tau (181P) CSF / Elecsys® β-Amyloid (1-42) CSF II Ratio

**pTau 181, Abeta 42 Ratio**

Elecsys® Total -Tau CSF / Elecsys® β-Amyloid (1-42) CSF II / Ratio

**Total Tau,  Abeta 42 Ratio**

There are also additional CSF biomarker tests on the market, however they are not currently FDA approved*

# Blood Biomarkers on the Horizon

| Tau | Amyloid-β | Neurodegeneration | Additional |
|---|---|---|---|
| pTau 217/npTau 217<br>pTau 181 | Aβ 42/40 | NfL | APOE<br>Vitamin's<br>TSH<br>Folate<br>Others |

Markers listed are examples of what blood tests can measure that are currently available in the clinic today

- While progress is being made toward Blood Biomarker Discovery, there are currently **no FDA-approved** blood biomarkers for Alzheimer's *

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

REVIEW ARTICLE

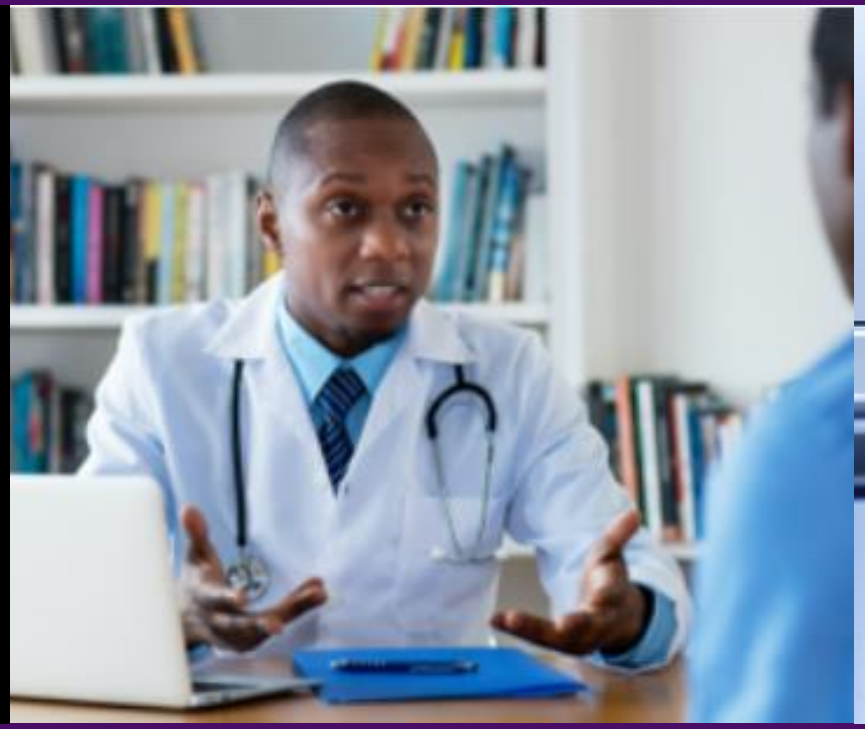
**The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease**

Oskar Hansson[1,2] | Rebecca M. Edelmayer[3] | Adam L. Boxer[4] | Maria C. Carrillo[3] | Michelle M. Mielke[5] | Gil D. Rabinovici[4] | Stephen Salloway[6] | Reisa Sperling[7] | Henrik Zetterberg[8,9,10,11,12] | Charlotte E. Teunissen[13]



*As of March 2024

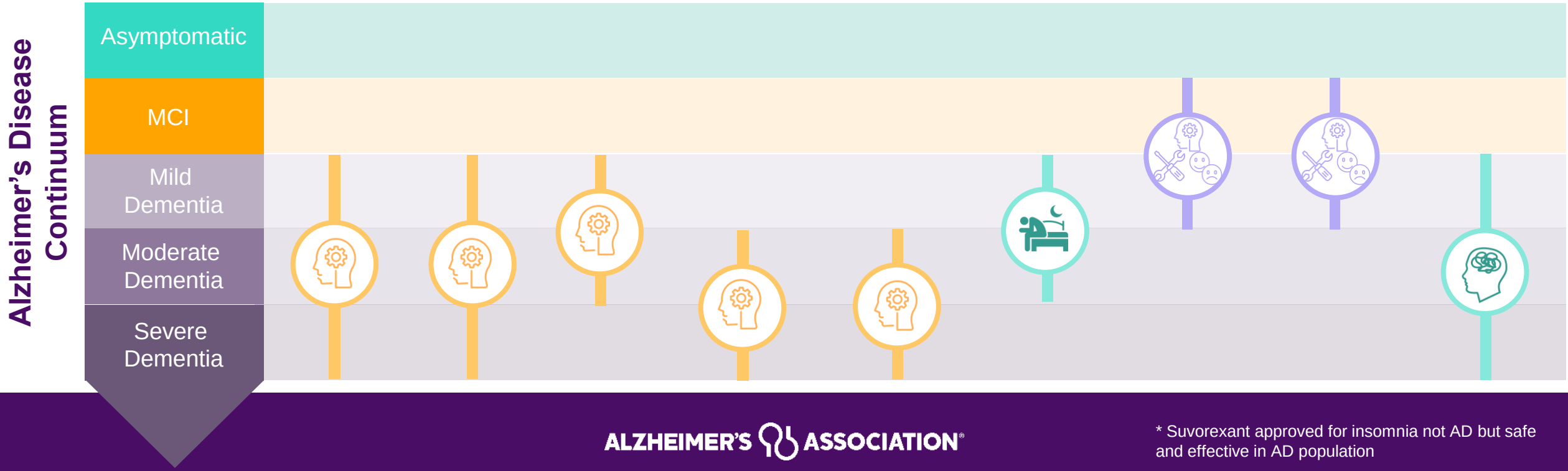
# Why is Early Detection so Important? Understanding the Treatment Landscape



ALZHEIMER'S ASSOCIATION®

# FDA Approved Therapies for Alzheimer's Disease

| First description of disease | Donepezil (Aricept) | Rivastigmine (Exelon) | Galantamine (Razadyne) | Memantine (Namenda) | Memantine + Donepezil (Namzaric) | Suvorexant* (Belsomra) | Aducanumab (Aduhelm) | Lecanemab (Leqembi) | Brexpiprazole (Rexulti) |
|---|---|---|---|---|---|---|---|---|---|
| 1906 | 1996 | 2000 | 2001 | 2003 | 2014 | 2020 | 2021 | 2023 | 2023 |
| | Treats Symptoms | | | | | Treats Symptoms | Slows Disease Progression | | Treats Symptoms |
| | Cognition & Function | | | | | Insomnia | Cognition, Function & Behavior | | Agitation |




ALZHEIMER'S ASSOCIATION®

* Suvorexant approved for insomnia not AD but safe and effective in AD population

# Medicines Focused on Behavioral and Psychological Symptoms of Dementia

## Brexpiprazole (Rexulti)

- First drug indicated for the treatment of Agitation Associated with Dementia Due to Alzheimer's Disease
- Submission was based on two Phase 3, 12-week, randomized, double-blind, placebo-controlled fixed-dose studies
- Primary endpoint was a change in agitation symptom frequency on the Cohen-Mansfield Agitation Inventory (CMAI)
- 31% greater reduction from baseline in frequency of agitation symptoms vs placebo



*Press Release: https://otsuka-us.com/news/otsuka-and-lundbeck-announce-us-food-and-drug-administration-fda-approval-supplemental-new*

# Deeper Dive:
# A New Phase of Treatment

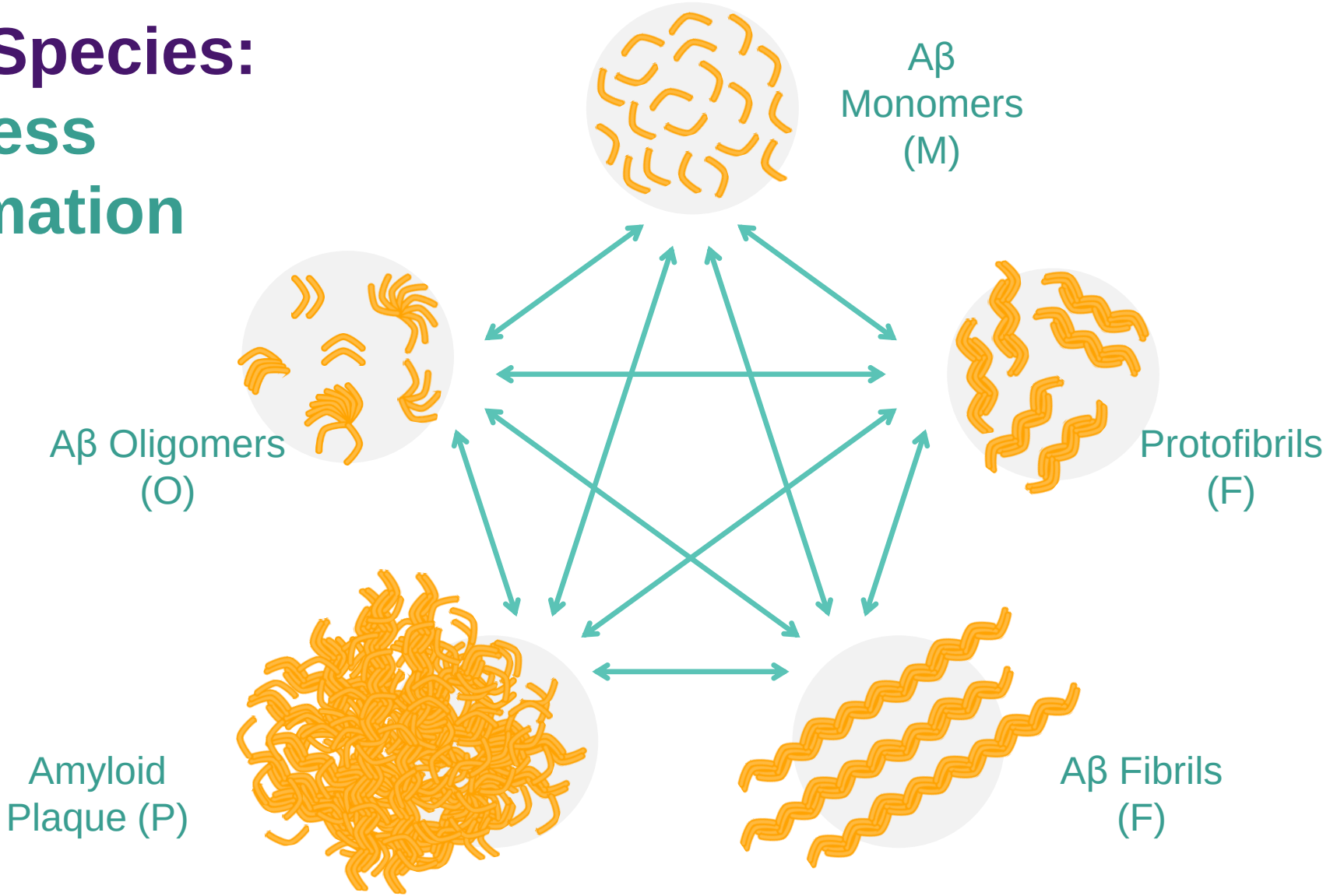
**Aducanumab (Aduhelm™)**
Approved in 2021
Targets Beta Amyloid

Limited Availability
Will be Discontinued

**Lecanemab (Leqembi ™)**
Approved in 2023
Targets Beta Amyloid

**Donanemab**
Pending FDA Review
2024
Targets Beta Amyloid

# Beta Amyloid Species:
## Dynamic Process of Plaque Formation

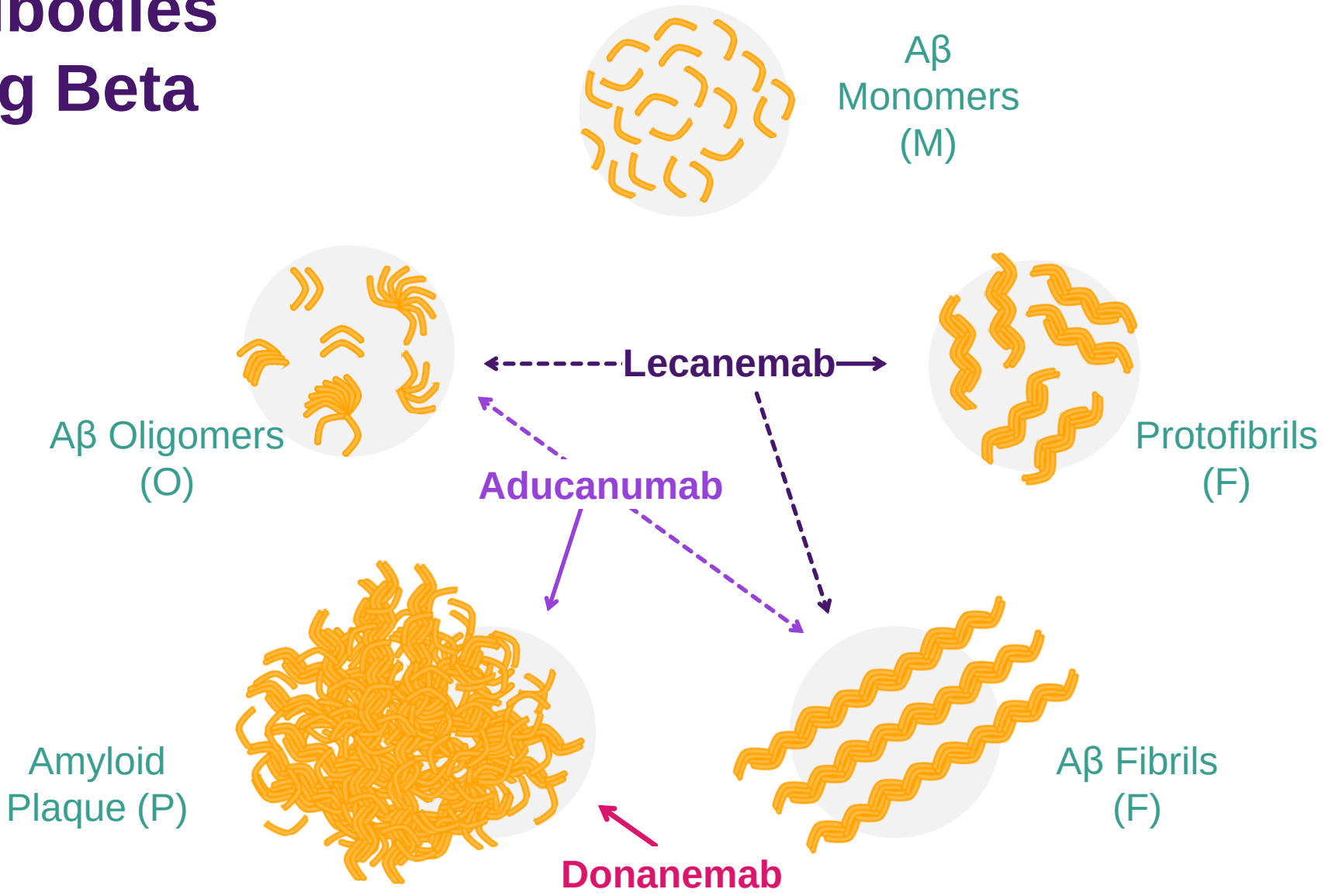



Cartoon Representation

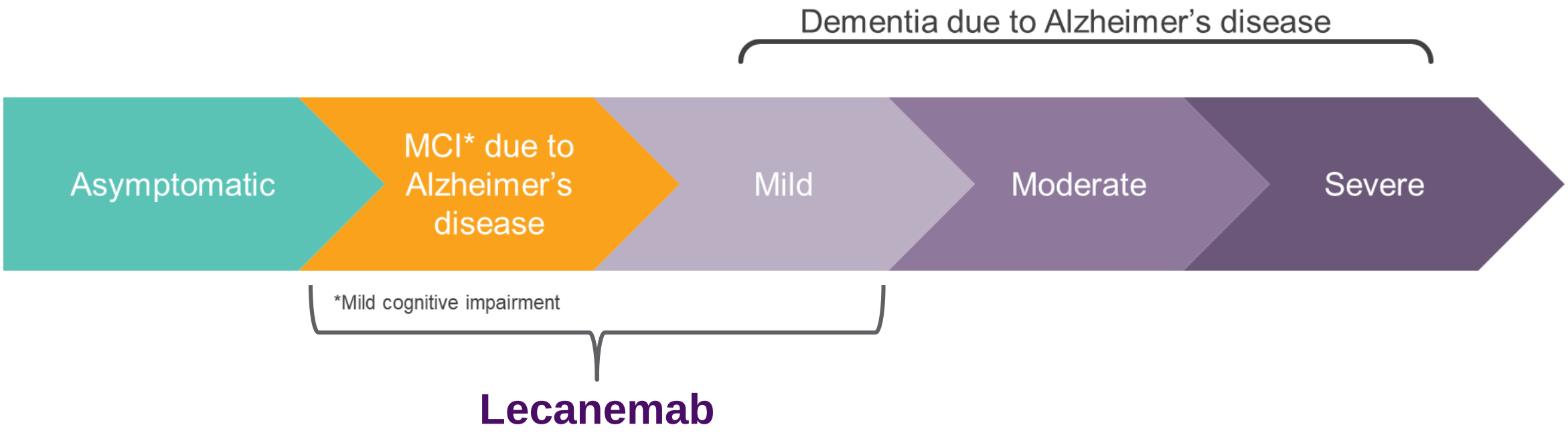
# Monoclonal Antibodies (mAbs) Targeting Beta Amyloid

strong binding ——————

weak binding - - - - - -



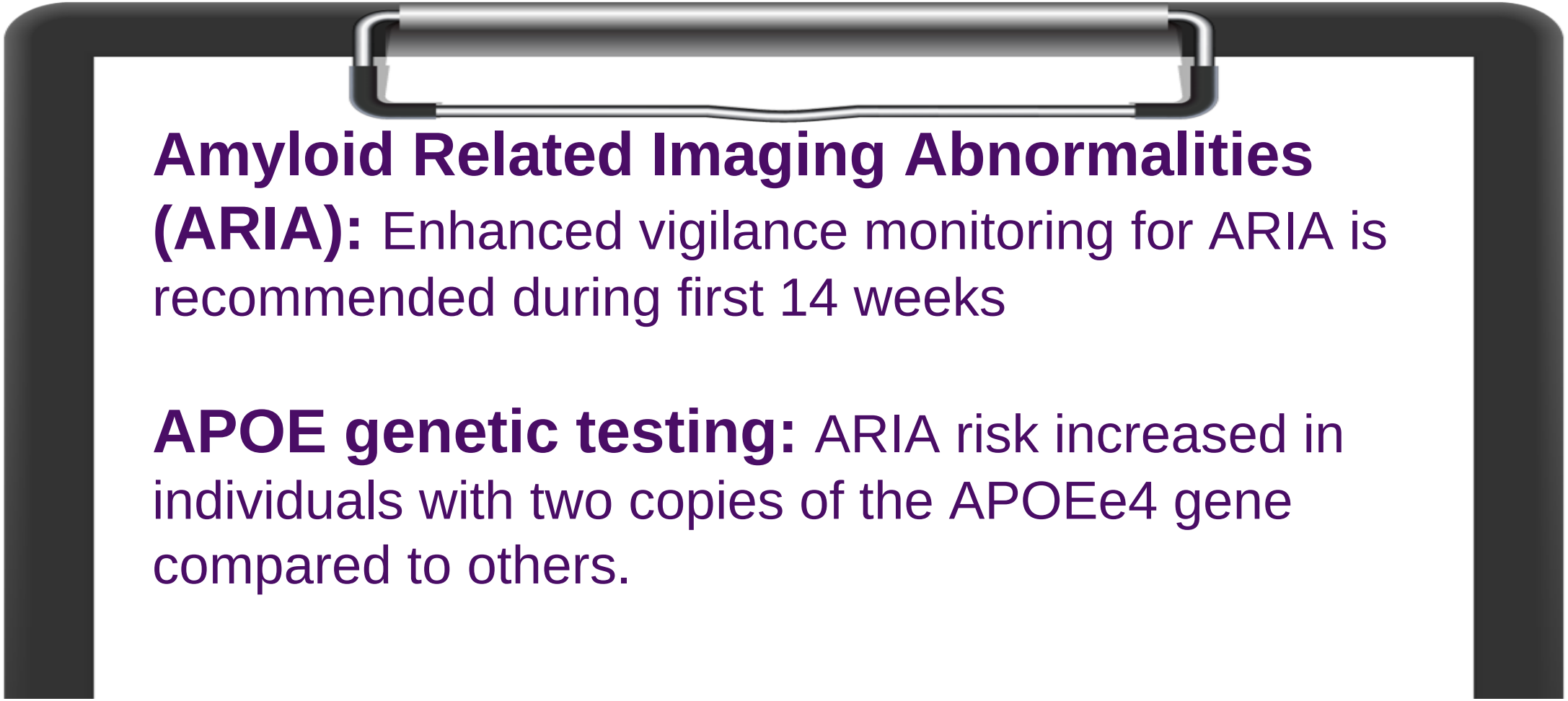
# Prescribing Information for Newly Approved Treatments




**Lecanemab**

- Ages 50-90
- Mild cognitive impairment (MCI) due to Alzheimer's OR mild Alzheimer's dementia
- Evidence of a buildup of amyloid plaques in the brain

# Prescribing Information for Newly Approved Treatments: Warnings & Precautions (Lecanemab label)



**Amyloid Related Imaging Abnormalities (ARIA):** Enhanced vigilance monitoring for ARIA is recommended during first 14 weeks

**APOE genetic testing:** ARIA risk increased in individuals with two copies of the APOEe4 gene compared to others.

# What is Clinically Meaningful?

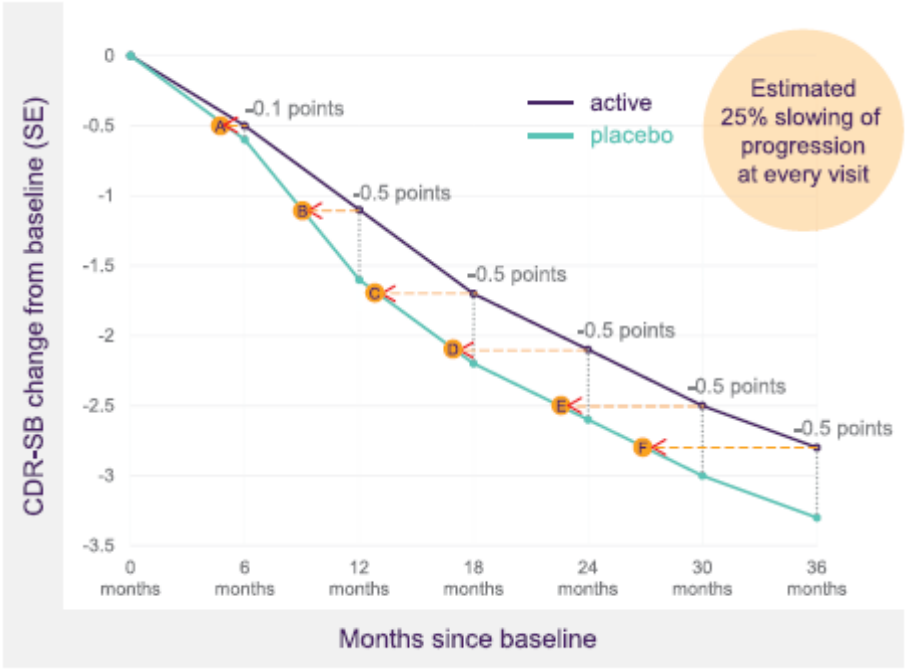
PERSPECTIVE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

## Expectations and clinical meaningfulness of randomized controlled trials

Ronald C. Petersen[1] | Paul S. Aisen[2] | J. Scott Andrews[3] | Alireza Atri[4] | Brandy R. Matthews[5] | Dorene M. Rentz[6] | Eric R. Siemers[7] | Christopher J. Weber[8] Maria C. Carrillo[8]

- Slowing the progression of Alzheimer's disease — rather than halting it, which may come eventually — has measurable and meaningful benefits for patients and their families, especially in early Alzheimer's when cognition and memory are mostly intact.
- Discussions on what is considered clinically meaningful change during a randomized controlled trial will help define our expectations of outcomes from therapeutic interventions in AD.




| | A | B | C | D | E | F |
|---|---|---|---|---|---|---|
| points | -0.1 | -0.5 | -0.5 | -0.5 | -0.5 | -0.5 |
| months difference vs. placebo | -1.5 | -3 | -4.5 | -6 | -7.5 | -9 |

**FIGURE 1** A progression model for repeated measures (PMRM), adapted from Raket,[26] illustrates the time savings between a CDR-SB change score at a specific time point and the slowing or delay of disease progression

# Leqembi (Lecanemab): Appropriate Use Recommendations

## Published in JPAD March 27, 2023 – Over 42K Downloads

J Prev Alz Dis 2023;3(10):362-377
Published online March 27, 2023, http://dx.doi.org/10.14283/jpad.2023.30

Review

### Lecanemab: Appropriate Use Recommendations

*J. Cummings[1], L. Apostolova[2], G.D. Rabinovici[3], A. Atri[4], P. Aisen[5], S. Greenberg[6], S. Hendrix[7], D. Selkoe[8], M. Weiner[9], R.C. Petersen[10], S. Salloway[11], For the Alzheimer's Disease and Related Disorders Therapeutics Work Group*

1. Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas (UNLV), Las Vegas, NV; USA; 2. Departments of Neurology, Radiology, Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA; 3. Memory and Aging Center, Department of Neurology, Weill Institute for Neurosciences and Department of Radiology and Biomedical Imaging; University of California, San Francisco, San Francisco, CA, USA; 4. Banner Sun Health Research Institute, Banner Health, Sun City, AZ; Center for Brain/Mind Medicine, Harvard Medical School, Boston, MA, USA; 5. Alzheimer's Treatment Research Institute, University of Southern California, San Diego, CA, USA; 6. Deparment of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; 7. Pentara Corporation, Millcreek Utah, USA; 8. Ann Romney Center for Neurologic Diseases, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; 9. Departments of Radiology and Biomedical Imaging, Medicine, Psychiatry and Neurology, University of California San Francisco, San Francisco, CA, USA; 10. Department of Neurology, Mayo Clinic, Rochester, MN, USA; 11. Butler Hospital and Warren Alpert Medical School of Brown University, Providence RI, USA

**Figure 1.** MRI monitoring for lecanemab

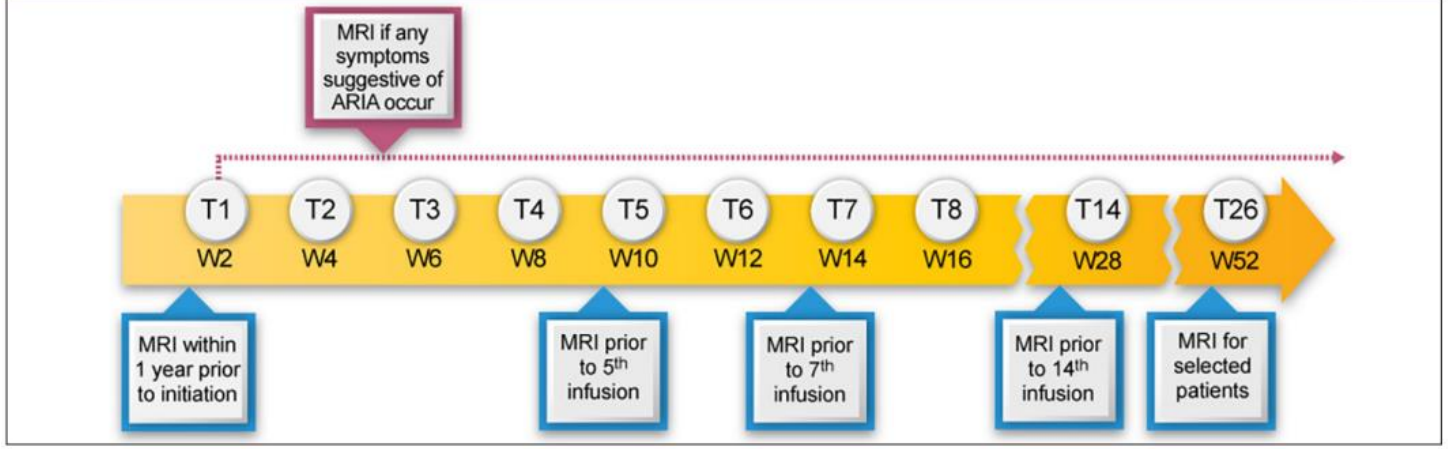
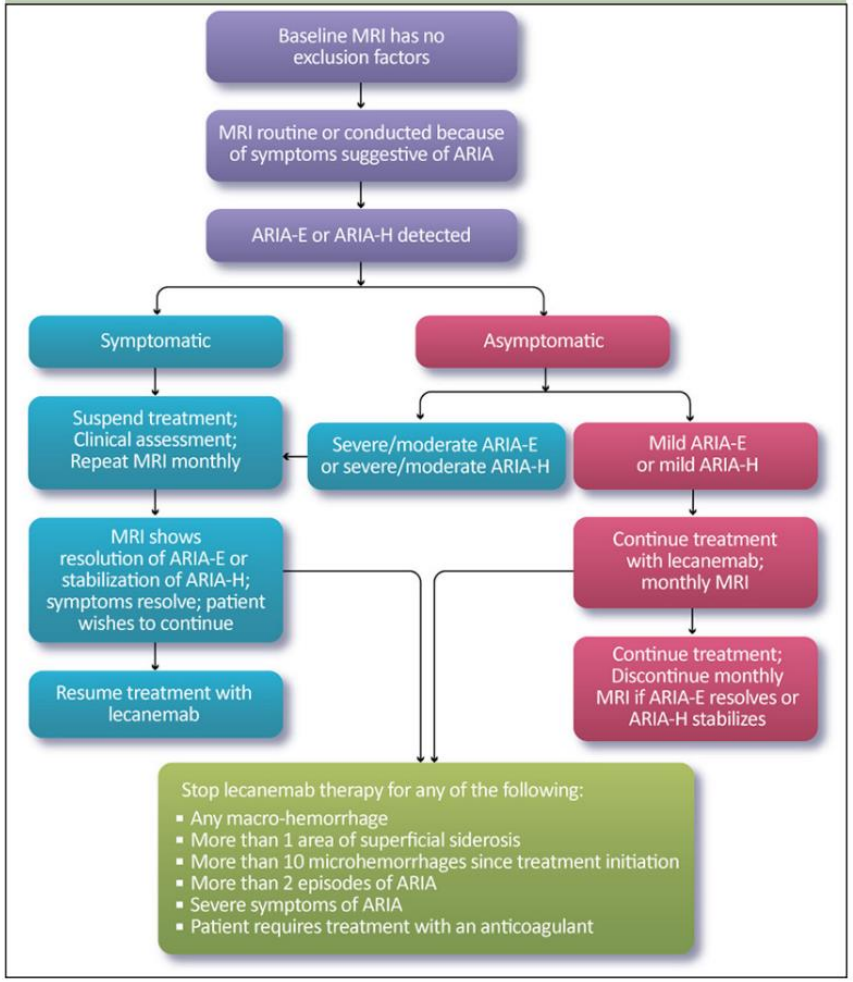



**Figure 2.** Monitoring and management of ARIA



# Leqembi (Lecanemab): Clinician Toolkit and Resources

## Based on Published Appropriate Use Recommendations

## Patient Eligibility Criteria

ALZHEIMER'S ASSOCIATION

| Lecanemab inclusion and exclusion criteria from CLARITY AD and proposed in the AUR | |
|---|---|
| **Eligibility Criteria Used in the CLARITY AD Pivotal Trial of Lecanemab** | **Eligibility Criteria for Lecanemab Treatment From the AUR** |
| **Inclusion Criteria (ie, required criteria for an individual to be considered)** | |
| Diagnosis of MCI or mild AD dementia | Clinical diagnosis of MCI or mild AD dementia[a] |
| Objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the WMS-IV LMII | Clinical diagnosis of MCI or mild AD dementia[a] |
| Positive biomarker for brain amyloid pathology | Positive amyloid PET or CSF studies indicative of AD |
| 50-90 years of age | Physician judgement used for patients outside the 50-90 year age range |
| MMSE score >22 at screening and baseline and <30 at screening and baseline | MMSE 22-30 or other cognitive screening instrument with a score compatible with early AD |
| BMI >17 and <35 at screening | Physician judgement used for patients at the extremes of BMI |
| If receiving an acetylcholinesterase inhibitor (donepezil, rivastigmine, galantamine) or memantine or both must be on a stable dose for at least 12 weeks prior to baseline | Patients may be on cognitive enhancing agents (donepezil, rivastigmine, galantamine, or memantine) for AD; patients may not be on aducanumab |
| Unless otherwise stated, participants must have been on stable doses of all other (that is, non-AD-related) permitted concomitant medications for at least 4 weeks prior to baseline | Patients may be on standard of care for other medical illnesses (see below for specifics regarding anticoagulation) |
| Have an identified study partner | Have a care partner or family member(s) who can ensure that the patient has the support needed to be treated with lecanemab |
| Provide written informed consent | Patients, care partners, and appropriate family members should understand the requirements for lecanemab therapy and the potential benefit and potential harm of treatment |

## Management of ARIA

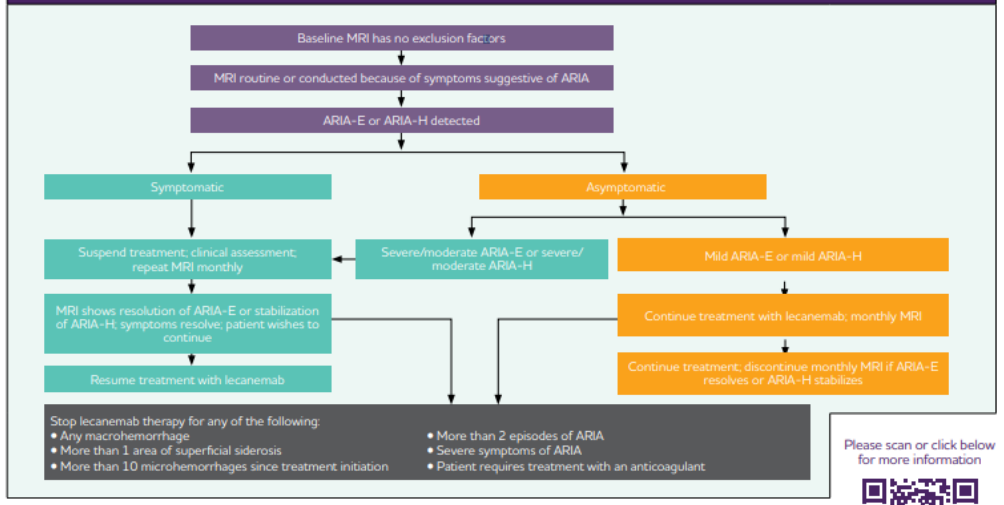
ALZHEIMER'S ASSOCIATION

In the CLARITY AD phase 3 trial of lecanemab, rates of ARIA for those on lecanemab were 12.6% for ARIA-E and 17.3% for ARIA-H vs 1.7% and 9.0%, respectively, for those on placebo.

**Description of mild, moderate, and severe radiographic ARIA (from the Prescribing Information)**

| ARIA Type | Radiographic Severity | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| ARIA-E | FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in 1 location <5 cm | FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm | FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/ independent sites of involvement may be noted |
| ARIA-H Microhemorrhage | ≤4 new incident microhemorrhages | 5 to 9 new incident microhemorrhages | 10 or more new incident microhemorrhages |
| ARIA-H Superficial Siderosis | 1 focal area of superficial siderosis | 2 focal areas of superficial siderosis | >2 areas of superficial siderosis |

**Monitoring and management of ARIA**




Please scan or click below for more information

AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA with edema; ARIA-H, ARIA with hemorrhagic changes; FLAIR, fluid attenuated inversion recovery; HCP, healthcare provider; MCI, mild cognitive impairment; MRI, magnetic resonance imaging.

Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis*. 2023;10(3):362-377. doi:10.14283/jpad.2023.30

# Donanemab Trial Shows Clear Slowing of Cognitive Decline

ALZHEIMER'S ASSOCIATION AAIC 23

## Unique aspects

1736 participants with early symptomatic AD with amyloid & low/medium or high tau

Half of participants met threshold of amyloid reduction to stop taking donanemab at 12 months

## Key Results

Study met primary and secondary endpoints

Donanemab slowed clinical decline by 35% and 40% in ability to perform activities of daily living

Greater benefit of donanemab in participants with low-medium tau (earlier stage of disease)

## Learnings

Early detection & intervention leads to greater benefit

Donanemab will significantly change the course of the disease

TRAILBLAZER-ALZ 2 clinical trial results of donanemab showed **significant slowing** of **cognitive** and **functional decline** in **early** symptomatic **Alzheimer's disease**

**Donanemab is currently pending FDA review and waiting for and Advisory Committee meeting date**

# A New Phase of Treatment

**Targets *amyloid***

**2021**

Aducanumab (Aduhelm™)

Will be discontinued 2024

**Targets *amyloid***

**2023**

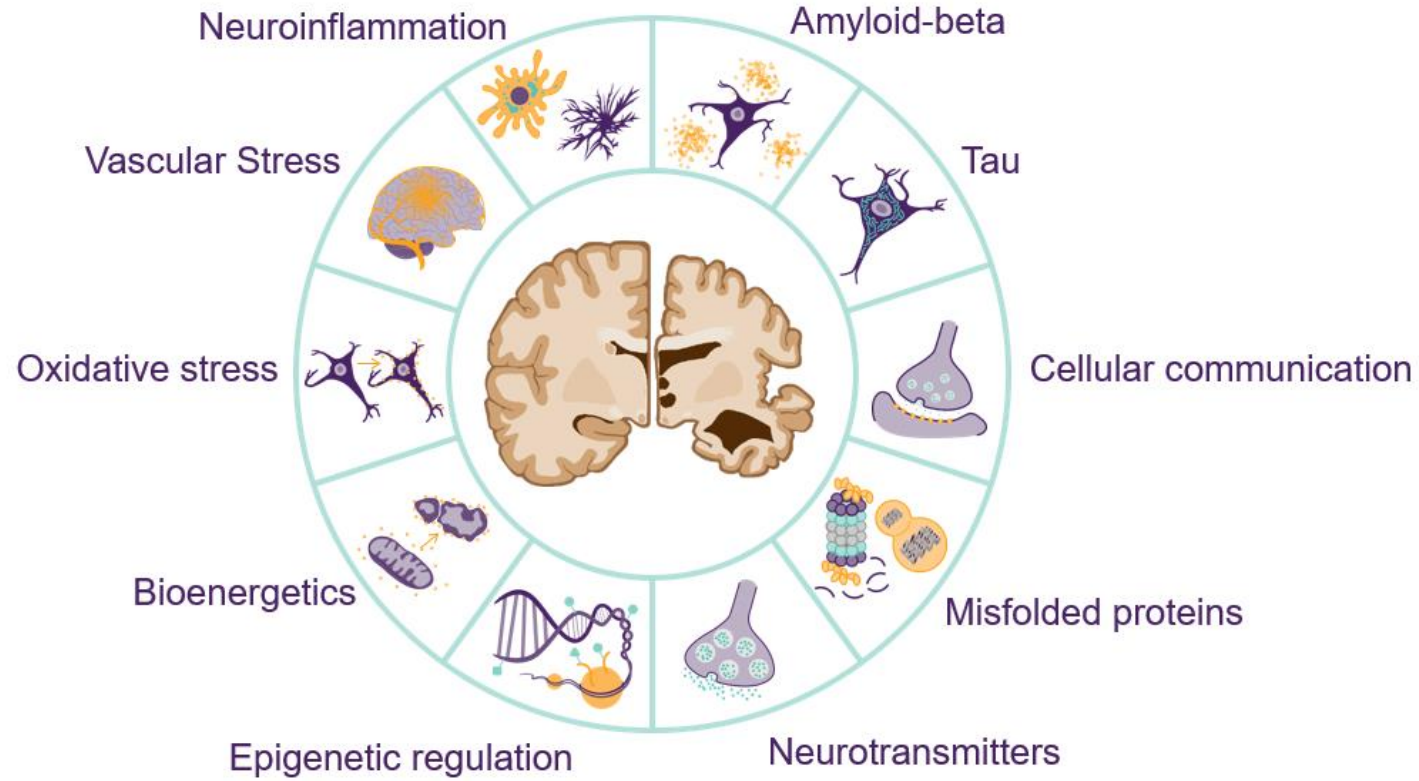
Lecanemab (Leqembi™)

**Targets *amyloid***

Donanemab

FDA review pending 2024

## Today, Over 140 Unique Therapies Being Tested in Clinical Trials that Target Multiple Aspects of Alzheimer's Biology



# ALZHEIMER'S DISEASE DRUG DEVELOPMENT PIPELINE: 2023

**In 2023**, there are

**141** UNIQUE THERAPIES in **187** CLINICAL TRIALS

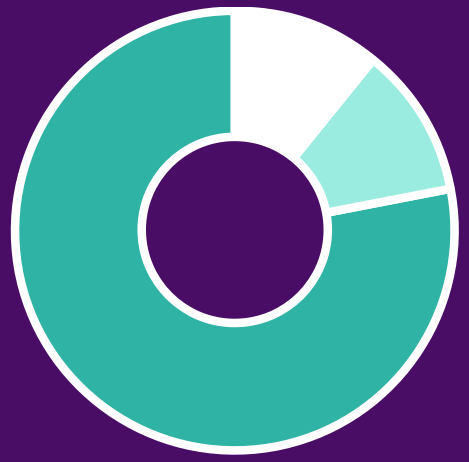
for Alzheimer's disease as registered on **clinicaltrials.gov**

**58** new agents have entered the pipeline in the past year

The total number of participants needed to populate all currently active trials (Phases 1, 2 and 3) is

**57,465**

## Targets of agents currently in clinical trials include



**78%** disease modification

**11%** cognitive enhancement

**11%** behavioral and neuropsychiatric symptoms

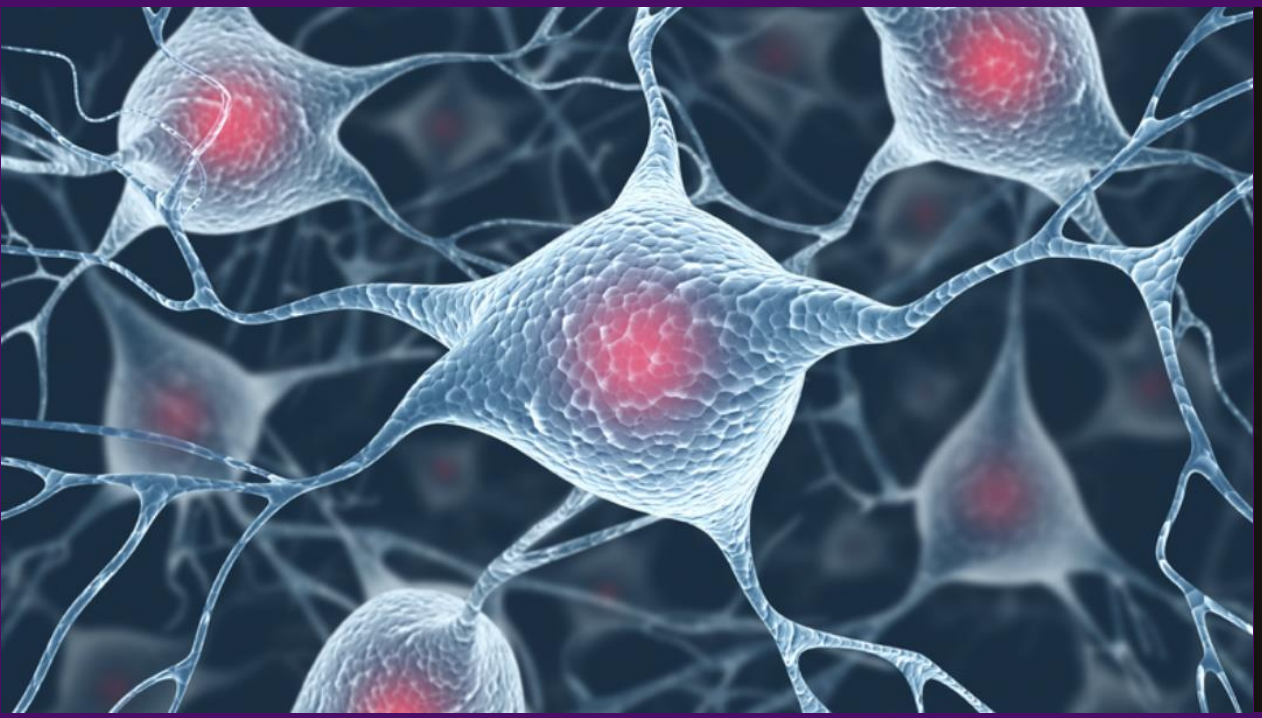
## Agents with primary mechanistic targets include

**72%** Novel disease processes

**28%** Amyloid and tau

Inflammation and synaptic plasticity are the most novel themes in the pipeline

# The Future of Alzheimer's and Dementia Diagnosis, Treatment and Care



ALZHEIMER'S ASSOCIATION®

ALZHEIMER'S NETWORK

# Alzheimer's Network for Treatment and Diagnostics (ALZ-NET):

A Real World Network to Inform the Future of Alzheimer's Research, Treatment and Care

**LAUNCHED AUGUST 2022**


ALZHEIMER'S ASSOCIATION®

# ALZHEIMER'S NETWORK

## ALZ-NET is building an integrated care network for ALL communities supported by real-world data.

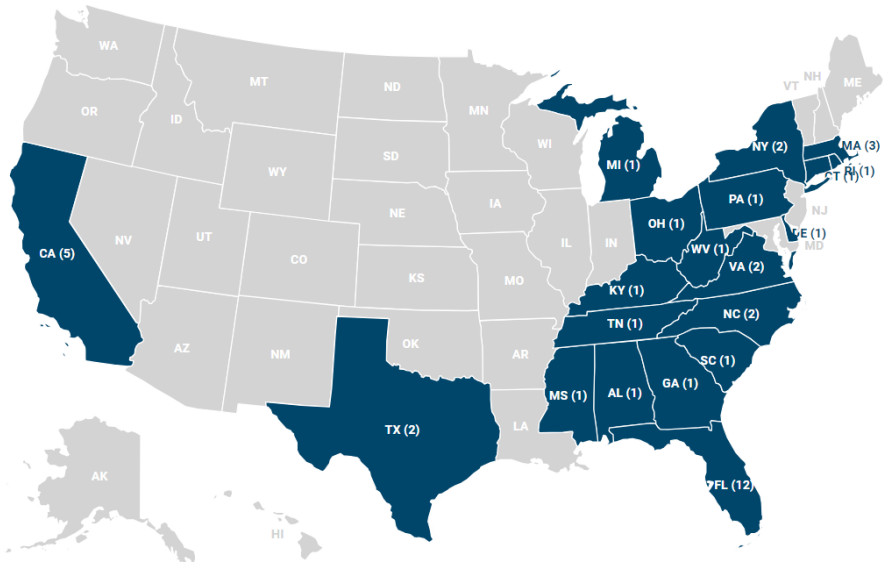
A **voluntary health care provider-enrolled patient network** that collects longitudinal data on patients being evaluated or treated for Alzheimer's disease.

Currently **enrolling patients being evaluated for or treated with novel Alzheimer's treatments** approved by the FDA in 2021 or after, including treatments that slow disease progression, or address cognition/function, or address neuropsychological/ behavioral symptoms.

Implemented in real-world clinical practice.
ALZ-NET is **not a clinical trial.**

## ALZ-NET will expand and evolve over time

## Over 190 sites in various stages of activation and start up




**Active Sites**
42

**Sites in Start Up**
125

**Sites in Queue**
26

**Patients Registered**
187

**Next Invitation Cycle**
March 2024

**As of 3/19/24*

ALZHEIMER'S ASSOCIATION®

For more information visit
**alz-net.org**

ALZHEIMER'S NETWORK

# What is ALZ-NET?

- Multi-site network that will **collect a minimum core set of regulatory-grade patient data** including diagnostic, treatment, measures of cognition, function and safety.
- **Collect, archive and share de-identified data** including demographic, medical, neurologic, imaging, biomarker, genetic and biospecimens.
- Can **collaborate with affiliated studies** conducted by academia, industry, federal or ALZ-NET study teams.
- **Track health outcomes and resource utilization** of participants to inform clinical care.

| ALZ-NET DATA COLLECTION | SITE START-UP[1] | CASE REGISTRATION[2] | BASELINE[3] | FOLLOW-UP[3] |
|---|---|---|---|---|
| Participating Site Characteristics | x | | | |
| Site Investigator (*Prescribing Clinician*) Characteristics | x | | | |
| Informed Consent | | x | | |
| Eligibility Assessment | | x | | |
| Patient Demographics | | x | | |
| Concurrent Study Enrollment | | | x | x |
| Patient Characteristics | | | x | o |
| Medical History | | | x | x |
| Lifestyle Data | | | x | o |
| Vital Signs | | | x | x |
| Clinical Features of Co-pathology | | | x | x |
| Additional Measures (*Cognitive, Functional, and Behavioral*) | | | x | x |
| AD Diagnosis, Characteristics, and Biomarkers | | | x | x |
| Brain Imaging Clinical Data[4] | | | x | x |
| Brain Image(s) Transmission[5] | | | x | x |
| Concomitant Medications | | | x | x |
| AD Treatment and Dosing Log | | | x | x |
| MRI Assessment | | | x | x |
| Healthcare Encounters (*Hospitalizations and ER Visits*) | | | x | x |
| Adverse Events (AEs) | | | x | x |
| End of Participation (Death, Lost to Follow up, Consent Withdrawn) – *only if applicable* | | | | x |

*x = Required form  o = Optional form*

ALZHEIMER'S NETWORK

Leveraging ALZ-NET to build RWE for diagnostics and treatments that support future innovative research and ultimately improve health equity and patient outcomes for Alzheimer's disease.

## Questions ALZ-NET could address:

- What is the long-term effectiveness of a treatment?
- What are long-term safety considerations?
- Who is most likely to respond well and benefit from different treatments?
- Who is most likely to have treatment-related side effects?
- How do new treatments interact with other medications people are taking?
- What happens when the available treatments target different aspects of the disease?
- Which treatments might work well together as combination therapies?
- And much more.

ALZHEIMER'S NETWORK

# ALZ-NET is a resource for the community

## Included in the Prescribing Information for Aducanumab (Aduhelm™) and Lecanemab (Leqembi™)

## WARNINGS AND PRECAUTIONS

### Monitoring and Dose Management Guidelines

The Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) is a voluntary provider-enrolled patient registry that collects information on treatments for Alzheimer's disease, including [ADUHELM or LEQEMBI]. Providers may obtain information about the registry at www.alz-net.org or contact alz-net@acr.org.

## PATIENT COUNSELING INFORMATION

### Patient Registry

Advise patients that the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) is a voluntary provider-enrolled patient registry that collects information on treatments for Alzheimer's disease, including [ADUHELM or LEQEMBI]. Encourage patients to participate in the ALZ-NET registry [see Warnings and Precautions (5.1)].

## MEDICATION GUIDE

### General information about the safe and effective use of [ADUHELM or LEQEMBI].

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about [ADUHELM or LEQEMBI] that is written for healthcare professionals. There is a registry that collects information on treatments for Alzheimer's disease. The registry is named ALZ-NET (Alzheimer's Network for Treatment and Diagnostics). Your healthcare provider can help you become enrolled in this registry

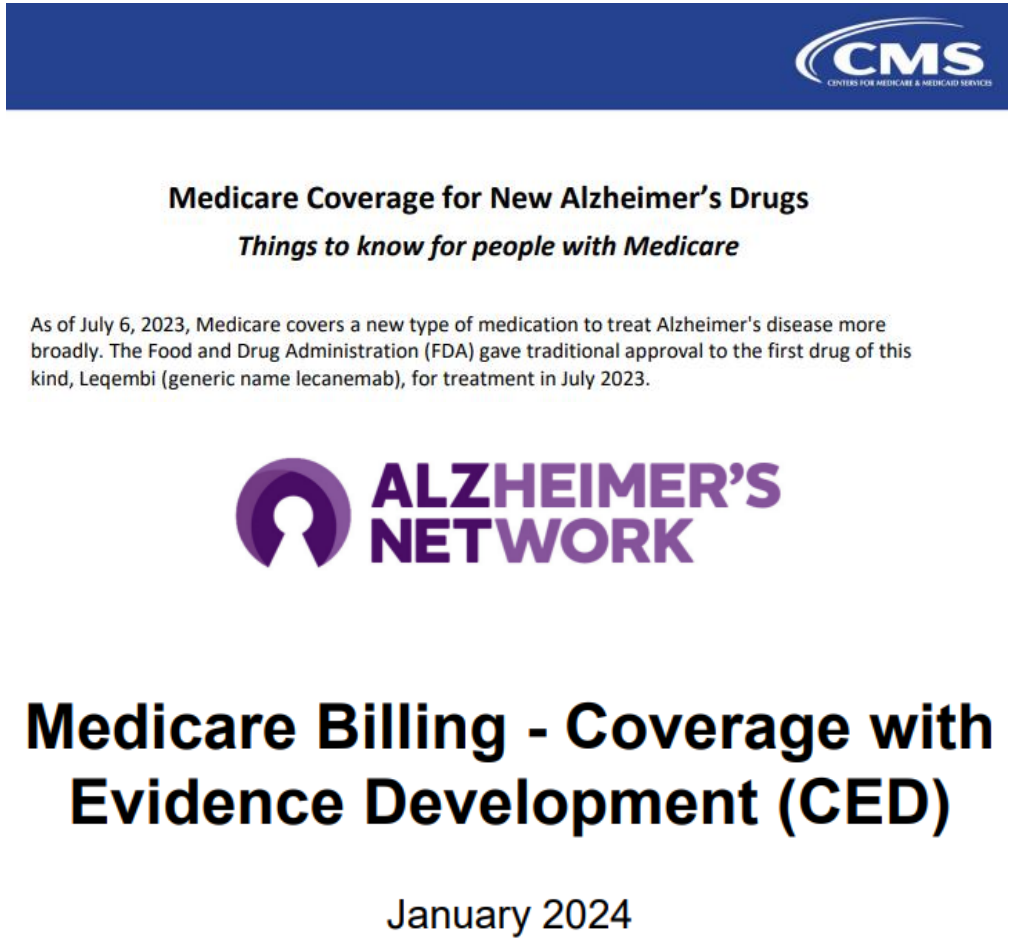
Information from:
https://www.leqembi.com/-/media/Files/Leqembi/Prescribing-Information.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761178s007lbl.pdf

ALZHEIMER'S ASSOCIATION®

For more information visit
**alz-net.org**

# ALZ-NET Affiliated Coverage with Evidence Development (CED) Study

- ALZ-NET is approved by the Centers for Medicare and Medicaid Services (CMS) as a Coverage with Evidence Development (CED) study and **can be used as a pathway to Medicare coverage for anti-amyloid Alzheimer's therapies** that have received traditional FDA approval.
- The principal purpose of the study is to investigate the long-term effectiveness and safety of new treatments and whether these treatments improve patient health outcomes.
- This is the first of ALZ-NET's affiliated studies that utilizes the infrastructure of the national ALZ-NET provider-enrolled patient registry protocol to conduct specific and detailed analysis on ALZ-NET data.



# Private Payers Also Including ALZ-NET as Registry Example

aetna®

## Leqembi™ (lecanemab-irmb) Medication Precertification Request

**Page 2 of 3**
(All fields must be completed and legible for precertification review.)

**Aetna Precertification Notification**
**Phone:** 1-866-752-7021 (TTY: 711)
**FAX:** 1-888-267-3277

**For Medicare Advantage Part B:**
Please Use Medicare Request Form

| Patient First Name | Patient Last Name | Patient Phone | Patient DOB |
|---|---|---|---|
| | | | |

**G. CLINICAL INFORMATION *(continued)*** – Required clinical information must be completed in its entirety for all precertification requests.

**For Initiation New Start Requests (clinical documentation required for all requests):**

**Alzheimer's Disease**

☐ Yes ☐ No Is the patient or provider currently participating in a provider-enrolled patient registry that collects information on treatments for Alzheimer's disease (e.g., Alzheimer's Network for Treatment and Diagnostics (ALZ-NET))?

Please indicate name of provider-enrolled patient registry: _____

United Healthcare®

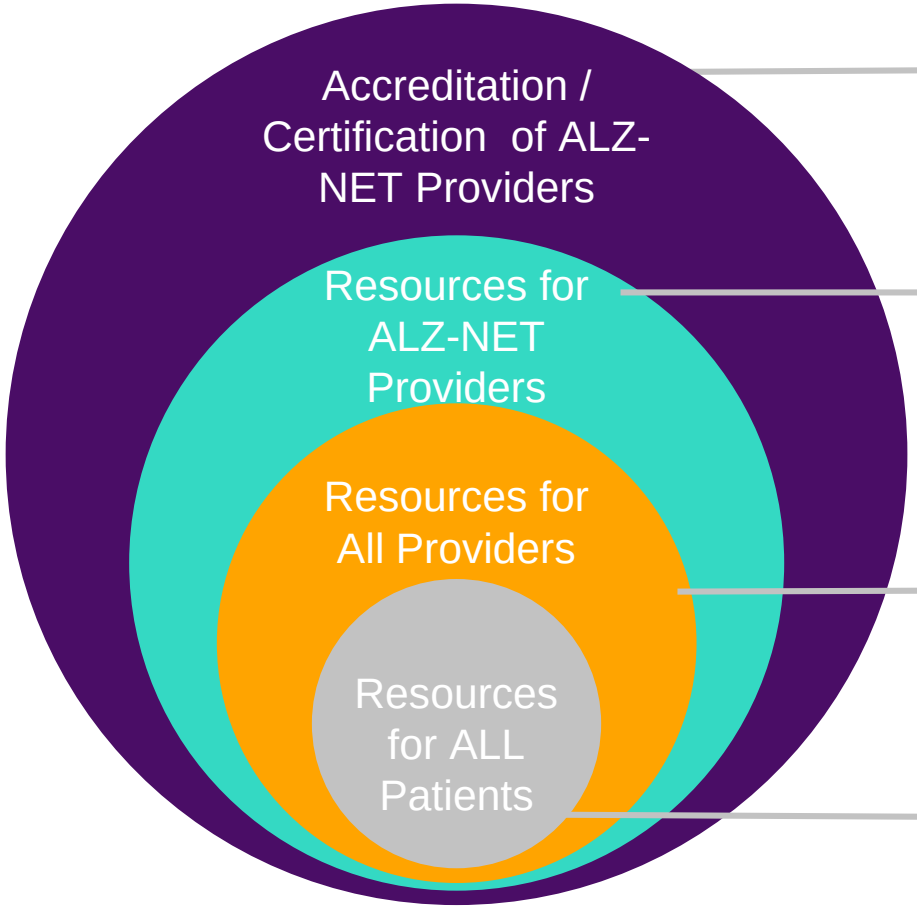
- Prescriber attests that the prescriber's site is currently registered or will seek registration with the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) or other comparable patient registry that collects information on treatments for Alzheimer's disease, including Leqembi; **and**
- Leqembi dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Initial authorization will be for no more than 6 months

For **continuation of therapy**, **all** of the following:

- Patient continues to have one of following diagnoses based on National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria[22,55]:
  - Mild cognitive impairment (MCI) due to Alzheimer's disease; **or**
  - Probable Alzheimer's disease dementia

ALZHEIMER'S NETWORK

# Creating an environment for better clinical care




- Site accreditation and certification for ALZ- NET providers
- Quality improvement programs, including reporting of site benchmarking in the context of local and national care standards

- Specially developed CME/CEU/training for all levels of staff of various specialties (e.g., NPs, APPs, neurologists, radiologists, and others)

- Compiled Guidelines/AUR/AUC for assessment, diagnosis, treatment, and care
- Access to CME, including material developed by ALZ Association, ASNR, ACR, and others
- Partner to enhance care and improve clinical outcomes

- Offer education and support resources for patients and families

ALZHEIMER'S NETWORK

ALZ-NET will lead the way through innovation and by building an integrated care network for ALL communities supported by real-world evidence (RWE).

**Improves provider practice**

**Increases quality care planning and treatment**

**Improve patient experience**

**Drive health equity through inclusive science**


**Addressing provider hesitancy**

**Reduces provider burden**

**Increases our comprehensive understanding**

**Accelerates ability to evaluate novel and combination therapies**

**Supports quality improvement strategies**

# In Summary…

- **Exciting time in research**
  - A paradigm shift for diagnosis and staging
  - New tools for detection and diagnosis
  - New approved treatments
  - Growing diversity of therapies under investigation
  - RWD / RWE are the next frontier
- **It is a NEW ERA of Research, Diagnosis, Treatment & Care**

Vision: A world without
**Alzheimer's disease**
**and all other dementia.™**

**1-800-272-3900**

**ALZ.ORG**

ALZHEIMER'S ASSOCIATION®